REMARKS

Claims 1, 2 and 5-20 are pending. Claims 6-8 and 11-20 have been withdrawn from consideration. Claims 1, 2 and 5 are rejected. It appears claim 9 has been allowed and claim 10 rejected, as further discussed below. Claim 5 is cancelled herein to pursue in a divisional application. No new matter is added. Applicants respectfully request reconsideration and withdrawal of all rejections.

Claim Rejections - 35 U.S.C. 103

Claim 10 (previously claim 8) is rejected under 35 U.S.C. 103 as being obvious over Merck Index #4852, Morikawa et al., Persson et al. and Chung et al. It is alleged that it is known to use indomethacin for treating inflammation and NO donors for increasing time to micturition and bladder pressure threshold, and that both compounds would be useful for treating urinary incontinence.

Applicants respectfully disagree.

Applicants note that while claim 10 has been rejected at page 3 of the Office Action, the Office Action Summary indicates that claim 10 has been allowed. However, it appears claim 9 has actually been allowed, since the Office Action also indicates that the Declaration of Dr. Piero Del Soldato, submitted on August 7, 2002, has been reconsidered and found convincing. *See* page 5 of the Office Action. This Declaration was submitted in order to demonstrate unexpected results for the compound of claim 9, that is, indomethacin (3-nitrooxymethyl)phenyl ester (i.e., indomethacin-NO), as compared to indomethacin alone. Applicants submit that if the Declaration is convincing with respect to indomethacin-NO, claim 9 must have been allowed.

Moreover, having pointed out that it is claim 9 that should be allowed, Applicants further submit that claim 10 should also be allowed by virtue of at least its dependency on claim 9. Applicants urge that claim 10 should be considered allowable since under U.S. patent law, the use of a novel, unobvious product in a claimed method is patentable subject matter. *See* MPEP 2116.01. Thus, the rejection of claim 10 appears to be mistaken and both claims 9 and 10 should be allowed. The rejection should be withdrawn.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 103 as being obvious over Scherrer et al. and Matji et al. in view of Persson et al. and Chung et al.

Applicants respectfully disagree.

It is alleged in the Office Action that it would have been obvious to combine two compounds, each of which is allegedly taught in the prior art as useful for the same purpose. However, Applicants would like to clarify that the invention of claims 1 and 2 (claim 5 having been cancelled to pursue in a divisional application) concerns neither a combination nor a composition of two active ingredients for achieving a therapeutic result, but rather a method of treating urinary incontinence by administering compounds of well defined structure as set forth in claim 1. The application contains no reference to the concept of combining two or more compounds as is alleged in the Office Action. Quite simply, the claimed invention concerns methods of treatment with certain compounds, a method not heretofore taught or suggested in any prior art.

Moreover, Applicants respectfully point out that those of ordinary skill in the art would find in the cited references no motivation to combine reference teachings, for example the teachings of Persson et al. and Chung et al., in order to obtain the claimed

invention. Applicants note that Persson et al. does disclose the administration of NO (in acidified solution of $NaNO_2$ and not as a group attached to an active molecule), but only with respect to possible involvement in relaxation induced by electric stimulation in pig isolated lower urinary tract smooth muscle. Chung et al. discloses the possibility of treating bladder instability and destrusor hyperreflexia by intravesical instillation of NO donors, but by exploiting the photo-induced adequate NP system. In other words, both references include further conditions that must be considered when evaluating the activity of NO donors, and whether multiple reference teachings should be combined. In the case of Persson et al. and Chung et al., the conditions are that without electric stimulation or UV light, respectively, the disclosed NO donors fail to work. Therefore, in view of such necessary conditions, those of ordinary skill in the art would have no motivation to combine reference teachings in an effort to arrive at something in accordance with the claimed invention. Moreover, even if those of ordinary skill in the art were to combine the teachings of the cited references, they most certainly would not arrive at a improved method of treating urinary incontinence as claimed.

Finally, Applicants would like to further demonstrate unexpected results concerning the treatment of urinary incontinence through the administration of specific compounds, as claimed. Applicants therefore submit herein another Declaration of Dr. Del Soldato, demonstrating that NO-flurbiprofen (compound (IX) of claim 1) is substantially more active than mere flurbiprofen in the treatment of urinary incontinence. As demonstrated at Table 1 of the Declaration, the administration of NO-flurbiprofen is able to improve bladder volume by more than twice as much when compared to the administration of mere flurbiprofen. Again, the claimed invention provides for

substantial and unexpected improvements with respect to the treatment of urinary incontinence.

Therefore, in view of the demonstrated unexpected results, and that the cited references are unable to teach or suggest the claimed invention, Applicants urge withdrawal of all rejections.

In view of the amendments and remarks above, Applicants submit that this application is in condition for allowance and request favorable action thereon.

In the event this paper is not timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper, referencing Attorney Docket No. 108907-09002.

Respectfully submitted,

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#33 RP 8/12/03

Attorney Docket No. P8907-9002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
P. Del Soldato, et al.	)	Examiner: Travers Russel
Serial No. 09/147,770	)	Group Art Unit: 1617
Filed: April 28, 1999	)	
For: NITRIC ESTER DERIVATIVES AND	)	
THEIR USE IN URINARY INCONTINENCE	)	
AND OTHER DISEASES	)	

DECLARATION OF DR. PIERO DEL SOLDATO

PURSUANT TO 37 C.F.R. § 1.132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, PIERO DEL SOLDATO, do hereby declare that:

1. I am one of the inventors of the invention claimed in the above-identified application Serial No. 09/147,770 ("Application").

2. Under my supervision, direction and control, the following compounds were tested in the pharmacological model of cystometry in conscious rats:

- Flurbiprofen
- The compound flurbiprofen 4-(nitrooxy)butyl ester, hereinafter called: "NO-flurbiprofen" prepared as described in Example 1, columns 6-7 (USP 5,621,000).

Two groups, A and B respectively (n. 8 animals/group) of Sprague Dawley rats (200-300 g body weight) were used. The rats were anaesthetised with Nembutal + chlorate hydrate i.p. The abdomen was then opened and the urinary bladder isolated. The bladder was then emptied and cannulated with a polyethylene cannula (Portex® PP30). One day after the

catheter implantation the rats were placed in Bollman' s cages. After a stabilization period of 20 min, the free tip of the cannula was connected to a pressure transducer and to a peristaltic pump. By said pump, at a rate of 0.1 ml/min it was infused a warm (37° C) saline solution into the urinary bladder. The basal bladder volume capacity was thus determined.

Bladder volume capacity (BVC), expressed as ml, is defined as the bladder volume at the time when detrusor contraction is followed by micturition.

It was found to be of 0.76 ml for group A and of 0.63 ml for group B.

Into the bladder was then infused a 0.1% acetic acid solution for 60 minutes to obtain an irritation of the bladder and a reduction of the BVC. At the end of said period of time the bladder volume capacity in group A was reduced to 0.32 ml and in group B to 0.27 ml. Said values were taken as BVC at t = 0.

Then group A was i.v. administered with flurbiprofen at a dose of 0.00123 mmol/Kg (0.3 mg/kg) and group B with the same amount on a molar basis of NO-flurbiprofen (0.44 mg/kg).

Infusion with the acetic acid solution was continued for one hour further.

The changes in BVC were monitored at 15, 30, 45 and 60 minutes after i.v. administration. Said changes are calculated as % bladder volume capacity changes vs BVC at t = 0.

Results are reported in Table 1.

3. I also declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false

statements and the like so made punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent or registration issuing thereon.

Table 1

% Bladder Volume Capacity change vs BVC at t=0 in an *in vivo* experimental of urinary incontinence by 0.1% acetic acid infusion in the bladder, followed by i.v. administration of a same molar dose (1.23×10^{-3} mmol/kg) of Flurbiprofen and NO-flurbiprofen				
Compound	**Bladder volume % change following i.v. administration of the compound vs t=0**			
	After 15 min	**After 30 min**	**After 45 min**	**After 60 min**
Flurbiprofen	**61.5**	**50.6**	**38.9**	**-17.1**
NO-flurbiprofen	**67.6**	**102.3**	**97.2**	**27.2**

Date: 31/07/2003 Signed: Piero Del Soldato